STATISTICAL ANALYSIS PLAN

NCT Number: NCT03439280

Study Title: A Phase 1/2a Open-label, Dose-Escalation Study to Investigate the Safety and Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of TAK-079 Administered Subcutaneously as a Single Agent in Patients With Relapsed/Refractory Multiple Myeloma

Study Number: TAK-079-1501

SAP Versions and Date:

Version 1.0: 11 January 2021

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PHASE 1/2a

Version: V1.0

Date: 11 January 2021

Prepared by:

[redacted], PhD

[redacted]

Based on:

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[redacted]

1.1 Approval Signatures

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Approvals:

[redacted], PhD
[redacted], Global Statistics — Date

[redacted]

2.0 TABLE OF CONTENTS

[redacted]

[redacted]

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANC	absolute neutrophil count
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete response
del	deletion
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	End of Treatment (visit)
FA	final analysis
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HR	Hazard Ratio
HU	health utilization
IA	interim analysis
IDMC	independent data monitoring committee
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IRC	independent review committee
ITT	intent-to-treat
K-M	Kaplan-Meier
line of therapy	1or more cycles of a planned treatment program; this may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner (eg, a planned treatment approach of induction therapy followed by autologous SCT, followed by maintenance is considered 1 line of therapy).[1] Typically each line of therapy is separated by progressive disease.
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
MM	multiple myeloma
MTD	Maximum tolerated dose

NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
PFS	progression-free survival
PK	pharmacokinetic(s)
PN	peripheral neuropathy
PR	partial response
PRO	patient-reported outcome
PSMB1	Proteasome subunit beta type-1
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RP2D	recommended phase 2 dose
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
SD	stable disease
t	translocation
TTP	time to progression
VGPR	very good partial response
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objective

Phase 1

The primary objective of the phase 1 portion of the study is to determine the safety and tolerability of TAK-079 monotherapy and when combined with a backbone regimen of PomDex in patients with RRMM.

Phase 2a

The primary objective of the phase 2a portion of the study is to provide a preliminary evaluation of the clinical activity of TAK-079 monotherapy in patients with RRMM.

4.2 Secondary Objectives

Phase 1

The phase 1 secondary objectives are:

- To investigate a potential MTD/RP2D of TAK-079 as a single agent and when added to a backbone regimen of PomDex.
- To evaluate the immunogenicity of TAK-079 as a single agent and when added to a backbone regimen of PomDex.
- To characterize the PK of TAK-079 as a single agent and when added to a backbone regimen of PomDex.
- To provide a preliminary evaluation of the clinical activity of TAK-079 as a single agent and when added to a backbone regimen of PomDex.

Phase 2a

The phase 2a secondary objectives are:

- To further evaluate safety at the MTD/RP2D.
- To provide a preliminary evaluation of time-to-event measures.
- To further evaluate the immunogenicity of TAK-079.
- To further characterize the PK of TAK-079.

[redacted]

4.3 Exploratory Objectives

[redacted]

4.4 Study Design

This is a multicenter, dose-escalation, open-label, single-arm, phase 1/2a study designed to determine the safety, tolerability, efficacy, PK, and immunogenicity of TAK-079 monotherapy in patients with RRMM, and to provide a preliminary assessment of its activity against MM.

The phase 1 portion of the study will evaluate administration of single agent TAK-079 for DLT(s) to determine the MTD/RP2D for further assessment in phase 2a. A recommended dose below the MTD may be identified based on safety, clinical, PK, [redacted] data. The safety and tolerability of TAK-079 will be assessed by recording and analyzing TEAEs from medical review of vital signs, physical examinations, serum chemistry and hematology analyses, urinalyses, ECGs, review of concomitant medications, dose modifications, and treatment discontinuations.

MM is a heterogenous disease requiring treatments across multiple lines of therapy despite recent advances. The pace of MM treatment has been rapid in recent years and even with a shift towards triplet regimens from doublet regimens, patients are still relapsing from, ineligible for, or intolerant to such combinations. Further the treatment paradigm is fragmented due to patient factors as well as disease factors and acceptance of recently approved regimens is gaining but remains variable. Therefore, this study will continue to evaluate patients with relapsed or refractory disease, including those who have not progressed following daratumumab, in an effort to more fully understand the activity of TAK-079 in patients who represent the highly heterogeneous population seen in current clinical practice. Before enrolling into the phase 2a phase of the study, additional patients will be enrolled in a dose Confirmatory Cohort to better understand the safety and clinical activity of the TAK-079 RP2D based on preliminary PK/[redacted] data.

More patients now receive combinations of lenalidomide, bortezomib, dexamethasone with or without daratumumab as first-line treatment, yet their disease still progresses. Most develop

[redacted]

lenalidomide-resistant disease; thus, alternatives to lenalidomide are required in later lines of therapy. Pomalidomide with dexamethasone is approved for patients following therapy with lenalidomide and a proteasome inhibitor; however, the duration of response is short (7.4 months) [20]. Evidence is emerging that adding an IV administered anti-CD38 agent to PomDex can help prolong response duration [23]. TAK-079, a SC administered anti-CD38 monoclonal antibody, is showing early signs of antimyeloma activity as a monotherapy in patients with advanced RRMM. Adding TAK-079 to the PomDex backbone could provide benefit to patients both in terms of improved antimyeloma activity over each agent alone, and would be more convenient to patients as compared with administration of IV administered anti-CD38 agents (ie, a TAK-079, a SC agent, added to the all oral PomDex regimen). Hence a new cohort will open to evaluate this combination. Information about the dose, safety, and activity of TAK-079 added to a standard backbone regimen of PomDex in patients with RRMM who have received at least 2 prior therapies and have demonstrated PD on or within 60 days of the completion of the last therapy will be collected.

The preliminary efficacy of TAK-079, as monotherapy and when added to PomDex, will be evaluated by measuring the ORR, defined as the proportion of patients who achieved a PR or better during study, as defined by IMWG (Appendix E; [21,22]). In addition, the efficacy of TAK-079 will be assessed by measuring MR, PFS, DOR, and OS; TTR will also be measured.

Once enrolled into the phase 1 Dose Escalation phase, patients will receive TAK-079 via SC administration in each 28 day cycle of treatment, administered as once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD. Patients will receive ongoing treatment with TAK-079 until they experience PD, unacceptable toxicities, or withdraw due to other reasons (see Section 6.3).

In the phase 1 Confirmation Cohort Phase, patients will receive TAK-079 via SC administration in each 28-day cycle of treatment, administered at a dose of 300 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and then once every 4 weeks thereafter until PD.

- In this cohort, up to 6 patients that are refractory to an anti-CD38 agent will be enrolled.
- Further in this cohort, approximately 12 patients that have RRMM disease (per prior therapy inclusion criteria Section 7.0) and are naïve to an anti-CD38 agent will be enrolled.

In the Combination Cohort, patients will receive TAK-079 via SC administration in each 28-day cycle of treatment, administered at a dose of 300 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and then once every 4 weeks thereafter until PD. PomDex will be administered according to the product labeling (Pomalyst UPSI, including Section 14.1).

- In this cohort, up to 6 patients will initially be enrolled. Safety in Cycle 1 will be reviewed in accordance with DLT definitions in Section 8.2.
- If 0 of 6 or 1 of 6 patients develop a DLT an additional 12 patients will be tested at the initial dose of TAK-079 [6 patients that are naïve to a prior anti-CD38 agent and 6 patients that have been exposed to a prior anti-CD38 agent], for an overall total of 18 patients.
- If 2 of 6 patients develop DLTs all available data will be reviewed before making

decisions about study conduct (See details in Section 8.5).

The Confirmation Cohort and the Combination Cohort may start in parallel and will run independently.

All cohorts will consist of the following phases/periods: screening, treatment, and follow-up:

- Screening period (visit 1): Days -21 to Day -1.
- Treatment period (visit 2/ongoing):
- Original dose Escalation Cohort: once-weekly treatment for 8 doses (Cycles 1 and 2), starting on Day 1, followed by treatment once every 2 weeks for 8 doses (Cycles 3-6), followed by treatment once every 4 weeks thereafter (Cycle 7 and beyond), continuing until patients experience PD, unacceptable toxicities, or withdrawal due to other reasons.
- Dose Confirmation Cohort: once weekly for 8 weeks in Cycles 1 and 2 (8 doses), once every 2 weeks for 16 weeks (8 doses) in Cycles 3 to 6, and once every 4 weeks thereafter (Cycles 7 and beyond) until PD.
- Combination Cohort: once weekly for 8 weeks in Cycles 1 and 2 (8 doses), once every 2 weeks for 16 weeks (8 doses) in Cycles 3 to 6, and once every 4 weeks thereafter (Cycles 7 and beyond) until PD. PomDex will be administered according to the product labeling (Pomalyst UPSI, including Section 14.1 describing dexamethasone dosing).
- Follow-up period (end of treatment [EOT] visit): Patients who discontinue study treatment will be followed for approximately 30 days after the last dose of study drug or until the start of subsequent alternative anticancer therapy to monitor safety/AEs. Patients who discontinue treatment for reasons other than PD will continue to be followed for PFS every 4 weeks from the EOT visit until PD, death, the start of subsequent anticancer therapy, study termination, or 12 months after discontinuation of study treatment, whichever occurs first. Patients who discontinue for PD will be followed for OS after the EOT visit. All patients will be followed for OS every 12 weeks until death, loss to follow-up, consent withdrawal, or study termination.

In phase 1, approximately 6 doses will be evaluated in ascending cohorts of 3 to 6 patients per cohort. Cohorts may be expanded by enrolling additional patients to further inform selection of the RP2D. Dose selection for phase 2a will take place after review of the available safety, efficacy, PK, [redacted] data obtained from the phase 1 portion of the study.

In the phase 1 dose Confirmatory Cohort, approximately 18 patients will be enrolled at 1 dose (300 mg); 12 patients will have been previously treated (see Section 7.0), up to 6 patients will have been previously treated and are refractory to an anti-CD38 therapy (see Section 7.0). In the Combination Cohort, approximately 18 patients will be enrolled who have received prior therapy and have demonstrated PD on or within 60 days of completion of the last therapy, note Section 7.0.

It is expected that approximately 100 patients will be enrolled in total for the phase 1 cohorts and phase 2a combined.

[redacted]

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary endpoints for phase 1 are:

- The number of patients with TEAEs overall and per dose level.
- Patients with DLTs at each dose level.
- Patients with Grade ≥ 3 TEAEs.
- Patients with SAEs.
- Patients who discontinue because of TEAEs.
- Patients with dose modifications (delays, interruptions, dose reductions).

The primary endpoint for phase 2a is:

- ORR, defined as the proportion of patients who achieved a partial response (PR) or better during the study as defined by International Myeloma Working Group (IMWG) Uniform Response Criteria.

5.2 Secondary Endpoints

The secondary endpoints for phase 1 are:

- RP2D based on both safety and efficacy outcomes as a single agent and when added to a backbone regimen of PomDex.
- Summary statistics for the following PK parameters as a single agent and when added to a backbone regimen of PomDex:
  - Maximum observed concentration (Cmax).
  - Time of first occurrence of Cmax (tmax).
  - Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUClast).
- Preliminary evaluation of antitumor activity of TAK-079, as single agent and in combination with PomDex, will be assessed for patients with MM by measuring:
  - ORR, defined as the proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria (Protocol [21,22]; Appendix E).
  - Proportion of patients who achieved a minimal response (MR), defined as 25% tumor reduction, including in patients with disease measurable by serum free light chains (FLCs) (Protocol [21,22]; Appendix E).
- Anti–TAK-079 antibody incidence and characteristics.

The secondary endpoints for phase 2a are:

- DLT-like frequencies and other TEAEs occurring over the course of extended treatment with TAK-079, including information about dose modification, treatment discontinuation, clinically significant laboratory values, and clinically significant vital signs.
- Summary statistics by dose level and cycle day for the following PK parameters: C_{max}, t_{max}, and AUC_{last}.
- Anti–TAK-079 antibody incidence and characteristics.
- Proportion of patients who achieved MR, defined as 25% tumor reduction.
- DOR, defined as the time from the date of first documentation of response to the date of the first documented PD.
- PFS, defined as the time from the date of first dose until the earliest date of PD, defined by IMWG criteria, or the date of death due to any cause.
- OS, defined as the date of first dose to the date of death due to any cause.
- TTR, defined as the time from the date of the first dose to the date of first documentation of response (PR or better).

5.3 Exploratory Endpoint

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

It is expected that approximately 100 patients will be enrolled in total for phase 1 and 2a combined. Once the RP2D is determined in phase 1, approximately 48 patients will be treated in phase 2a to provide a preliminary estimate of the ORR in patients with RRMM.

A 3+3 dose escalation schema will be used for dose escalation as described in Section 4.4

A group of 3 to 6 patients will be enrolled in each TAK-079 dose cohort based on safety, clinical, PK, [redacted] data. Each patient will participate in only 1 dose cohort. The actual dose levels may be adjusted based on the observed safety profile.

Additional patients may be enrolled in a limited cohort expansion to confirm the safety and receptor occupancy on tumor cells before the phase 2a of this study is opened to enrollment. In the phase 1 dose Confirmatory Cohort, approximately 18 patients will be enrolled at 1 dose and schedule: 12 patients with RRMM that is anti-CD38 naive and up to 6 patients with RRMM that is refractory to an anti-CD38 therapy. In the Combination Cohort, approximately 18 patients with RRMM that has been previously treated with at least 2 prior therapies and that is refractory to the last therapy will be enrolled.

In phase 2a, up to a total of 48 patients will be treated to provide a preliminary estimate of the ORR in 2 expansion cohorts of patients with RRMM: up to 24 patients with RRMM that is anti-CD38 naive and up to 24 patients with RRMM that is refractory to an anti-CD38 therapy. Phase 2a of the study will also provide a more robust estimate of the safety profile to determine whether the MTD is appropriate for future studies as the RP2D.

No prospective calculations of statistical power have been made; however, Table 6.a shows the width of the 80% CI, based on the observed ORR in a cohort size of 24 patients, for a range of observed response rates.

Table 6.a 80% Confidence Interval Based on the Observed ORR

[redacted]

N = 24 patients.
ORR: overall response rate.

[redacted]

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be conducted using SAS® Version 9.2, or higher.

Where appropriate, variables will be summarized descriptively by study visit. For categorical variables, the count and proportions of each possible value will be tabulated by treatment group. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, standard deviation (SD), minimum, and maximum values will be presented by treatment group. For time-to-event data, the Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their confidence intervals (CIs).

Means and medians will be presented to 1 more decimal place than the recorded data. SDs and CIs about a parameter estimate will be presented to 2 more decimal places than the recorded data.

All confidence intervals, statistical tests, and resulting P-values will be reported as 2-sided and will be assessed at α=0.05 significance level unless otherwise stated. P-values will be rounded to 3 decimal places prior to assessment of statistical significance.

The summary tables will be presented for each dose cohort, combination cohorts, pooled cohorts in phase 1 portion, RP2D cohort, and all patients.

Baseline values are defined as the last observed value before the first dose of study medication.

7.1.1 Study Definitions

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first full dose of the medication. Other study days are defined relative to Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.3 Definition of Study Visit Windows

All data will be categorized on the basis of the visit at which they are collected. Visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF). Summaries will be provided for scheduled visits only.

7.1.4 Conventions for Missing Adverse Event Dates

Adverse events with start dates that are completely or partially missing will be imputed as follows:

- If month and year are known but day is missing
    - If month and year are the same as month and year of 1st dose date, then 1st dose date will be imputed.

[redacted]

- If month and year are different than month and year of 1st dose date, then 1st date of the month will be imputed.

- If year is known but day and month are missing
  - If year is same as year of 1st dose date, then 1st dose date will be imputed.
  - If year is different than year of 1st dose date, then 1st of January of the year will be imputed.
- If all is missing, then 1st dose date will be imputed.

Imputing missing AE start date is mandatory. After imputation, all imputed dates are checked against the stop dates to ensure that start dates do not occur after stop dates. If an imputed start date occurs after the stop date, then change the imputed start date to be the same as the stop date.

Adverse events with stop dates that are completely or partially missing will be imputed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed.
- If year is known, but day and month are missing
  - If YYYY < year of last dose, then 31st of December will be imputed.
  - If YYYY = year of last dose, then 31st of December will be imputed.
  - If YYYY > year of last dose, then 1st of January will be imputed.
- If all are missing, then 31st of December in the year of last dose will be imputed.

Imputing missing AE stop date is not mandatory if AE is regarded as ongoing. However if it is to be done, the rules are outlined above. If subject dies, then use death date for AE stop date.

After imputation, all imputed dates are checked against start dates to ensure that stop dates do not occur before start dates. If an imputed stop date occurs prior to the start date, then change the imputed stop date to be the same as the start date.

7.1.5 Conventions for Missing Concomitant Medication Dates

Subsequent therapies recorded as concomitant medications with missing/partial start dates will be imputed as follows:

- When month and year are present and the day of the month is missing,
  - If the month and year of the start date are the same as the month and year of treatment termination, the day of treatment termination or the day-component of the stop date, whichever comes first, is imputed.

- If the start month and year are not the same as the month and year of treatment termination, the first day of the month is imputed.

When only a year is present or no components of the start date are present, the date will not be imputed.

7.2 Analysis Sets

All-enrolled analysis set: The all-enrolled analysis set will include all patients enrolled into the study, regardless of whether they received any dose of any study drug.

DLT-evaluable analysis set: The DLT-evaluable analysis set will include patients who receive all Cycle 1 doses of TAK-079 and have completed Cycle 1 procedures, or experience a DLT in Cycle 1 in the phase 1 portion of the study. The DLT-evaluable population will be used to determine the RP2D/MTD.

Safety analysis set: The safety analysis set will include all enrolled patients who receive at least 1 dose of any study drug.

Response-evaluable analysis set: The response-evaluable analysis set is a subset of the safety analysis set including patients with measurable disease at baseline and at least 1 posttreatment evaluation. The response-evaluable population will be used for the analyses of response rates, TTR, and DOR.

[redacted]

PK analysis set: The PK analysis set will include those patients from the safety analysis set who have sufficient dosing data and TAK 079 concentration-time data to permit the calculation of PK parameters.

Immunogenicity analysis set: The immunogenicity analysis set will include those patients from the safety population who have baseline and at least one postbaseline sample assessment.

7.3 Disposition of Subjects

The disposition of patients includes the number of patients in the following categories: patients enrolled at each dose level during dose escalation, patients in each of the study population except PK and Immunogenicity analysis sets, patients completed treatment per protocol, patients completed study per protocol, patients ongoing on treatment, patients off treatment, primary reason off treatment, patients ongoing on follow-up, patients off study during follow-up, and primary reason off study during follow-up. Percentages will be presented for each dose cohort, combination cohorts, pooled cohorts in phase 1 portion, RP2D cohort, and all patients.

A listing will present data concerning patient disposition.

[redacted]

7.4 Demographic and Other Baseline Characteristics

Demographics

Demographics will be summarized by each dose cohort in a descriptive fashion in the ITT population. Demographic data at study entry to be evaluated will include age, sex, race, ethnicity, height, weight and ECOG status.

Disease Specific History

Disease specific history will be summarized to include type of immunoglobulin at diagnosis, Durie-Salmon stage at diagnosis, International Stage System (ISS) at diagnosis, evidence of lytic bone disease and extramedullary disease, prior therapies (number of patients with prior therapy, lines of prior therapies, best hematological response to prior therapy, type of prior therapy in the format of therapy contained, number of patients who received anti-CD38 monoclonal antibody [e.g., daratumumab, isatuximab] as the last line of prior therapy, number of patients refractory to any line of prior therapy, prior radiation site and dose, prior surgery), and months from prior diagnosis to the first dose of TAK-079. Disease specific history will be summarized and listed by cohorts and for all patients if there is sufficient data for analysis. The months from prior diagnosis to the first dose of TAK-079 is calculated by

$$\frac{\text{first dose date - date of diagnosis}}{365.25/12}$$

Disease specific characteristics will be presented in by-patient listings.

Baseline characteristics

Baseline disease characteristics will be summarized by cohorts and for all patients including serum M-protein, urine M-protein, serum free light chain, serum free light chain ratio, β_2-microglobulin and its category (i.e., < 2.5, 2.5-5.5, > 5.5 mg/L), serum creatinine and its category, (<=2, >2 mg/dL), calculated creatinine clearance and its category (<30, 30-<60, 60-<90, >=90 mL/min), serum albumin by category (i.e., <3.5, >=3.5 g/dL), corrected calcium, hemoglobin, platelet count, neutrophil count, LDH and Eastern Cooperative Oncology Group (ECOG) performance status.

Creatinine clearance will be calculated using the Cockcroft-Gault formulas as follows:

For male patients:

$$\text{creatinine clearance} = \frac{(140 - \text{Age[yrs]}) \times \text{weight[kg]}}{72 \times (\text{serum creatinine[mg/dL]})}$$

For female patients:

$$\text{creatinine clearance} = 0.85 \times \frac{(140 - \text{Age[yrs]}) \times \text{weight[kg]}}{72 \times (\text{serum creatinine[mg/dL]})}$$

Integer values will be used.

[redacted]

For patients with heavy chain, the patient's type of myeloma is determined by the combination of heavy chain type (IgG, IgA, IgM, IgD, and other) and light chain type (Kappa, Lambda, and biclonal). In descriptive summaries, the disease will be categorized by the heavy chain type first, then within each of these categories, patients will be further classified according to their light chain type. For patients with light chain only, patients will be classified according to their light chain type.

Extent of disease and bone marrow cytogenetic results at baseline

The extent of disease at baseline will be summarized including number of patients with a bone marrow aspirate, bone marrow aspirate results (% plasma cells), number of patients with a bone marrow biopsy, bone marrow biopsy results (% plasma cells, % cellularity, type of cellularity, % Kappa/Lambda ratio performed), skeletal survey results (normal, abnormal not clinically significant, abnormal clinically significant, and not done) and imaging including magnetic resonance imaging (MRI) / computed tomography (CT) results (normal, abnormal not clinically significant, abnormal clinically significant, and not done), number and percentage of lytic bone lesions present, number of extramedullary plasmacytoma present, size of measurable plasmacytoma (longest diameter and longest perpendicular) and site of extramedullary plasmacytoma.

Bone marrow cytogenetic results at baseline from the conventional/karyotype and molecular/FISH cytogenetic analyses methods will be displayed. The results will be categorized as "Normal", "Abnormal" and "Indeterminate". The percentage of each category will be summarized. Abnormal types of interest, including but not limited to, del 13, del 17, t(4;14), t(11;14), t(14;16), -13q, -17p, hyperdiploidy, hypodiploidy and high risk cytogenetics group (del 17, -17p, t(4,14) or t(14,16)), will also be tabulated.

By-patient listings for these baseline characteristics will also be presented.

7.5 Medical History and Concurrent Medical Conditions

General medical history data including prior therapies, prior radiation, prior surgery and prior transplant will be summazied. A by-patient listing will also be presented.

7.6 Medication History and Concomitant Medications

Concomitant medications will be coded by generic term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO drug generic term from the first dose of study treatment through 30 days after the last dose of study medication. Concomitant procedures will not be coded.

Concomitant medications and procedures will be presented in by-patient listings and summazied table.

[redacted]

7.7 Study Drug Exposure and Compliance

A patient will be considered as treated in a cycle as long as this patient received any amount of study drug in that cycle. A treatment cycle is defined as a cycle in which the patient received any amount of study drug.

Relative dose intensity is defined as 100*(dose intensity (mg/week)/ planned dose intensity (mg/week)), where dose intensity is defined as (total amount of dose taken (mg) / treatment duration (weeks)) and planned dose intensity = (total planned amount of dose taken (mg) / planned treatment duration (weeks)). An RDI of 100% indicates that the drug was administered at the right dose within the planned timeframe (e.g. every 28 days).

The exposure to study drug will be summarized including the extent of exposure in days, number of cycles, total amount of dose taken (in mg), total number of doses taken, number and percentages of patients by treatment cycles, and relative dose intensity. Aggregate summary of numbers and percentages of patients who had 1-6, 7-12, and ≥13 treatment cycles will also be presented in the same table. Test dose will be excluded from exposure calculations and summaries.

The number of patients with 100% relative dose intensity, 80% to < 100%, 50% to <80%, and <50% will be summarized by dose level and for all patients.

All the summazied tables will be presented by TAK-079, Pomalidomide and Dexamethasone separately. Dosing data will also be presented in a by-patient listing.

7.8 Efficacy Analysis

All available efficacy data will be included in data listings and tabulated by each dose cohort, combination cohorts, pooled cohorts in phase 1 portion, RP2D cohort, and all patients. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures. In general, missing data will be treated as missing, and no data imputation will be applied, unless otherwise specified.

Response will be assessed according to the International Myeloma Working Group (IMWG) criteria for all patients. Best M-Protein Response to Treatment is defined as the percent change from baseline to best (lowest) value post-baseline in serum M-protein for subjects with measurable serum M-protein at baseline; for subjects with non-measurable serum M-protein but measurable urine M-protein, it is the percent change from baseline to best (lowest) value post-baseline in urine M-protein. Best M-Protein Response to Treatment will be tabulated by categories of % reduction (e.g., 100 % reduction, >=90% reduction, >=50% reduction, 90%-100% reduction, 75-90% reduction, 50%-75% reduction, 25%-50% reduction, <25% Reduction to <25% Increase, >=25% Increase). No Post-Baseline Assessment of Measurable M-Protein will also be tabulated.

Overall Response Rate

The ORR is defined as the proportion of patients who achieved a confirmed PR or better during study per investigator assessment; sCR, CR, VGPR, and PR as defined by IMWG Uniform

Response Criteria [1]. The ORR is determined from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. To calculate the confirmed response, 1 visit after end of treatment (EOT) is used to confirm the assessment at EOT. ORR will be summarized by frequencies and percentages.

Duration of Response (DOR)

Duration of response is defined as the time from the date of first documentation of a confirmed PR or better to the date of first documentation of PD for responders. Responders without documentation of PD will be censored at the date of their last response assessment that is SD or better and prior to initiation of alternative therapy.

Progression Free Survival (PFS)

PFS is defined as the time from the date of first dose until the sooner of the date of PD, defined by IMWG criteria, or the date of death due to any cause. Patients without documentation of PD or death will be censored at the date of the last response assessment that is SD or better prior to the date of initiation of alternative therapy. Patients with no response assessment will be censored at the date of first dose.

Overall Survival (OS)

OS is defined as the date of first dose to the date of death due to any cause. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive.

Time to Response (TTR)

Time to response is defined as the time from first dose to the date of first documentation of response (PR or better).

Time to Best Response

Time to response is defined as the time from first dose to the date of first instance of confirmed best response.

Time to Progression (TTP)

TTP is defined as the time from first dose to time of progressive disease.

In general, time-to-event data will be summarized by 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% confidence intervals, as well as the KM estimate at 6, 9, 12, 18 and 24 months. In addition, the percent of censored observations with reasons will also be summarized.

The response rates, DOR, time to response, and time to best response will be analyzed based on Response-Evaluable analysis sets. PFS and OS will be analyzed based on safety analysis sets. Time-to-event endpoints will be analyzed using standard survival analysis techniques based on Kaplan-Meier estimates.

[redacted]

The duration of follow-up is defined as time from the date of first dose of study treatment to the death or last known visit. If a subject dies, the duration is equal to date of death minus first dose date + 1 with censor variable =1 (censored for follow-up). If a subject is alive, the duration is equal to the date subject last known to be alive minus study start + 1 with censor variable=0 (event for follow up).

7.9 Pharmacokinetic/[redacted] Analysis

7.9.1 Pharmacokinetic Analysis

PK parameters will be estimated using noncompartmental methods with Phoenix WinNonlin. The PK parameters will be estimated from the concentration-time profiles for the PK population. The following PK parameters will be determined, as permitted by data:

- $C_{max.}$
- $t_{max.}$
- AUC_{∞}.
- $AUC_{last.}$

PK parameters will be summarized using descriptive statistics. Individual TAK-079 concentration-time data and individual PK parameters will be presented in listings and tabulated using summary statistics by dose cohort. Individual and mean concentration-time profiles will be plotted by dose cohort.

The PK data collected in this study may also contribute to future population PK analyses of TAK-079. These population PK analyses may include data collected in other TAK-079 clinical studies. The analysis plan for the population PK analysis will be separately defined, and the results of these analyses will be reported separately.

Similarly, the time-matched PK and triplicate ECG data collected in this study may contribute to future concentration-QT interval corrected for heart rate (QTc) analyses. These analyses may include data collected in other TAK-079 studies. The analysis plan for the concentration-QTc analysis will be separately defined, and the results will be ported separately.

7.9.2 [redacted]

[redacted]

7.10 Other Outcomes

7.10.1 Immunogenicity Analyses

The proportion of subjects with positive ADA (transient and persistent) during the study will be summarized. The proportion of patients in phase 2a with positive neutralizing ADA during the study may be summarized. The effect of immunogenicity on PK, safety, and efficacy will be examined. NABs may also be assessed in patients.

The immunogenicity of TAK-079 will be assessed by determining anti–TAK-079 antibody incidence and characteristics (eg, titer, transiently, and persistently ADA, and possibly neutralizing activity). Analysis will be based on available data from patients with a baseline assessment and at least 1 post-baseline immunogenicity assessment (from the immunogenicity analysis set). Summaries will be provided separately for each study phase and by dose, as applicable. The incidence of immunogenicity will be calculated. The impact of anti–TAK-079 antibodies on the PK profile, drug efficacy, and clinical safety will be evaluated, if possible. These analyses will be exploratory in nature, and all results will be descriptive in nature.

7.11 Safety Analysis

7.11.1 Adverse Events

Adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug. Treatment-emergent is defined as any AE that occurs after administration of the first dose of any study treatment through 30 days after the last dose of any study treatment.

All AEs will be presented in a by-patient listing. AEs will be tabulated according to the MedDRA by system organ class, high level terms and preferred terms. Summary tabulations by each dose cohort, combination cohorts, pooled cohorts in phase 1 portion, RP2D cohort, and all patients will be provided for the following categories:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs (also grade 3 only and 4 only will be reported separately)
- Grade 3 or higher drug-related treatment-emergent AEs (also grade 3 only and 4 only will be reported separately)
- The most commonly reported treatment-emergent AEs (i.e., those events reported by >= 10% of all patients)
- Serious adverse events related and regardless of relationship

- Treatment-emergent AEs resulting in study drug reduction
- Treatment-emergent AEs resulting in any study drug discontinuation

Patients with the same AE more than once will have that event counted only once within each body system, once within each high level term, and once within each preferred term. Patients with the same AE more than once will have the maximum intensity of that event counted once within each body system, once within each high level term, and once within each preferred term.

Drug-related treatment-emergent AEs will also be summarized by the National Cancer Institute Common Toxicity Criteria (NCI CTCAE) version 4.03 AE [2].

Most commonly reported (at least 10% of all patients) treatment-emergent AEs will be presented by preferred term only. Patients with the same AE more than once will have that event counted only once within each preferred term.

An overall summary AE table will include numbers and percentages of patients who had any AE, drug-related AE, grade 3 or higher AE, grade 3 or higher drug-related AE, serious AE (SAE), drug-related SAE, AE resulting in any drug discontinuation, AE resulting in any dose reduction, AE resulting in any dose modification (defined as delay, interruption, reduction or discontinuation), and on-study deaths. On-study death is defined as the death that occurs between the first dose of study drug and up to 30 days after the last dose.

Serious Adverse Events

The number and percentage of patients experiencing at least one treatment-emergent SAE will be summarized by MedDRA primary system organ class, high level term, and preferred term. Drug-related SAEs will be summarized similarly.

In addition, a by-patient listing of the SAEs will be presented (the patient listing will contain all SAEs regardless of treatment-emergent AE status).

Deaths

A by-patient listing of the on-study deaths will be presented. On-study death is defined as the death that occurs between the first dose of study drug up to 30 days after the last dose of study drug.

Adverse Events Resulting in Discontinuation of Study Drug

The number and percentage of patients experiencing at least one adverse event resulting in discontinuation of any study drug will be summarized by MedDRA system organ class, high level term, and preferred term.

A by-patient listing of treatment-emergent AEs resulting in discontinuation of any study drug will be presented. All AEs resulting in discontinuation of any study drug occurring on-study will be displayed.

[redacted]

Adverse Events Resulting in Dose Reduction, Increase, Delay or Interruption

The number and percentage of patients experiencing at least one adverse event resulting in any dose reduction will be summarized by MedDRA system organ class, high level term, and preferred term.

A by-patient listing of AEs resulting in dose reduction/increase/delay/interruption of any study drug will be presented. All AEs resulting in dose reduction/increase/delay/interruption of any study drug occurring on-study will be displayed.

Dose Limiting Toxicities (DLTs)

A by-patient listing of DLTs that occur during Cycle 1 of treatment will be presented by dose level and for all patients enrolled during the dose escalation portion of this study. Patients will be grouped by the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower or higher dose level.

7.11.2 Clinical Laboratory Evaluations

All laboratory values will be converted to standardized units and summarized in tables and listings by cohort, dose level, and overall. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier. However, for the bone marrow plasma cell percentage, the convention as (x-1)% (mainly for < 5% for CR) will be used.

Laboratory test results from the central laboratory will be used when they are available. Laboratory test results from local laboratory will only be used when no central laboratory test results exist at the same scheduled sample collection time point.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used.

Laboratory test results will be summarized according to the scheduled sample collection time point. Change from baseline will also be presented. Unscheduled laboratory test results will be listed and included in laboratory shift tables. The parameters to be analyzed are as follows:

- Hematology: hemoglobin, hematocrit, neutrophils (ANC), platelets counts, and leukocytes with differential
- Serum chemistry: blood urea nitrogen (BUN), creatinine, total bilirubin, urate, lactate dehydrogenase (LDH), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, calcium, sodium, potassium, chloride, bicarbonate or carbon dioxide (CO_2), magnesium, phosphate, and Gamma glutamyl transferase (GGT), Standard C-reactive protein.

Shift tables will be constructed for laboratory parameters to tabulate changes in NCI CTCAE for toxicity (version 4.03) from study entry to post study entry worst CTC grade. Parameters to be tabulated will include:

- Hematology: ANC, hemoglobin, platelets,
- Serum chemistry: ALT, AST, ALP, creatinine, total bilirubin, calcium, magnesium, potassium, sodium, and phosphate.

Summary statistics will also be presented for shift from urinalysis values at study entry.

- Urinalysis: Turbidity and Color, pH, specific gravity, protein, ketones, bilirubin, occult blood, nitrite, urobilinogen, glucose, leukocytes, microscopic analysis

Mean laboratory values and box plots over time for key lab parameters will be produced, including but not limited to ANC, platelets, and liver function tests (ALT, AST, alkaline phosphatase, and total bilirubin).

By-patient listings to be presented include hematology, serum chemistry, urinalysis, urine total protein, and urine creatinine.

7.11.3 Vital Signs

The actual values of vital sign parameters including temperature, blood pressure, heart rate, and body weight, will be summarized over time by cohort, dose level, and overall. Change from baseline will also be presented.

A by-patient listing will also be presented.

7.11.4 12-Lead ECGs

Descriptive statistics for the actual values and changes from baseline in ECGs will be listed by time point and summarized by cohort, dose level, and overall. Standard and triplicate ECGs will be summarized separately.

Rate-corrected QT interval (millisec) of electrocardiograph (QTc) interval will be calculated using Bazett's correction and Fridericia's correction. The formulas are:

$$QTc\ (Bazett) = QT / (RR^{0.5})$$

$$QTc\ (Fridericia) = QT / (RR^{0.33})$$

where RR = 60 / heart rate (bpm)

7.11.5 Other Observations Related to Safety

Eastern Cooperative Oncology Group performance status and shifts from baseline to post-baseline assessment over time, and ECOG score frequency table over time will be summarized by cohort, dose level, and overall. Shifts from baseline to the worst post-baseline score will be tabulated by cohort, dose level, and overall. Injection related reaction evaluation and severity will be summarized by table using safety analysis set and be listed. Pregnancy testing results will be presented in a by-patient listing.

7.12 Interim Analysis

An interim analysis of phase I part may be conducted as needed.

[redacted]

7.13 Changes in the Statistical Analysis Plan

{None}

8.0 REFERENCES

1. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia 2006; 20(9): 1467-73.
2. U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. 14 June 2010.

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	11-Jan-2021 16:02 UTC